IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Kenneth Chien, et al. Art Unit : 1645
Serial No. : 09/830,779 Examiner : Patricia Ann Duffy
Filed : November 30, 2001
Title : A METHOD OF INHIBITION OF PHOSPHOLAMBAN ACTIVITY FOR THE TREATMENT OF CARDIAC DISEASE AND HEART FAILURE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

1. I, Kenneth Chien, am an expert in the field of molecular biology and cardiac disease and was an expert at the time of the invention. I am a co-inventor of the above-referenced patent application and I am presently employed as a professor at the University of California, San Diego, CA, assignee of the above-referenced patent application. My resume is attached as documentation of my credentials.

2. The specification presents data that demonstrates that PLB inhibitor molecule linked (using, for example, polylysine) to a transport peptide (e.g., an antennapedia transport peptide) can induce enhanced contractility in a cardiac cell. For example, Example 4, pages 28 to 29, provides data that demonstrates that a mutant PLB molecule linked to a transport molecule via polylysine was efficiently translocated into isolated rat cardiomyocytes. These cardiomyocytes showed enhanced contractility. The results of these experiments are illustrated in Figures 5a and 5b.

CERTIFICATE OF MAILING BY "FIRST CLASS MAIL"

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, MS RCE, P.O. Box 1450, Alexandria, Virginia 22313-1450, on May 20, 2004.

Jeanne Amour

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3. Example 5, including Table 3, pages 29 to 31, of the above-referenced patent application describes experiments that administer a mutant PLB linked to a transport peptide to mouse cardiomyocytes. Table 3 summarizes data from those experiments. As noted on page 31, lines 9 to 11, of Example 5, while there appeared to be a trend towards a larger, faster contraction in the myocyte, T-test analysis did not identify any statistical difference due to the high variability of the data. However, while the results of Example 5's experiments were inconclusive, the totality of the experimental evidence described in this specification overwhelming and conclusively demonstrate that exogenous mutant PLB can inhibit the activity endogenous PBL to improve cardiac contractility. Furthermore, knowledge accrued since the filing of the specification confirms that exogenous mutant PLB can inhibit the activity endogenous PBL to improve cardiac contractility.

4. The level of skill in this art at the time of the invention was very high. Screening procedures used to identify protocols to effectively apply and administer exogenous PLB protein were all well known in the art and at the time this application was filed. Using the teaching of the specification, one skilled in the art could have selected routine screening protocols known in the art at the time of the invention to determine means to effectively apply and administer exogenous PLB protein. Using the teaching of the specification, one of skill in the art could have determined appropriate protocols to apply and administer an exogenous PLB linked to a transport protein to successfully practice the claimed methods of the invention.

5. An exemplary dominant negative PLB is described, inter alia, in Example 4, page 28, lines 24 to 26, as a cargo peptide derived from the first 16 residues of PLB, or, SEQ ID NO:8. This cargo sequence could also have been derived from any segment of wild-type PLB or mutant PLB. Determining additional dominant negative PLB species could have been determined by the skilled artisan using routine screening methods, including the exemplary methods described in the specification.

6. The term "dominant negative" was well known in the art at the time of the invention and the specification uses the term as it would have been understood to one skilled in

the art at the time of the invention. For example, an example of a textbook definition for "dominant negative protein" now, and at the time of the invention (the definition has not changed) is "a mutant protein that as a result of the mutation has lost activity or function and interferes with the function of its corresponding wild-type protein." Thus, at the time of the invention, and now, the skilled artisan understand that a "dominant negative protein" is a mutant protein that as a result of the mutation has lost activity or function and the mutant protein interferes with the function of its corresponding wild-type protein.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted

Date:_____ _____

Kenneth Chien